REMARKS

Prior to the present amendment, claims 17-59, 67, 68, 70-73, 76-80 and 82-86 were pending. Of the pending claims, claims 19, 21-59, 80, and 82-84 were withdrawn by the examiner as being drawn to non-elected inventions. By the present amendment, claims 17, 18 and 85 have been amended. Accordingly, claims 17, 18, 20, 67, 68, 70-73, 76-79, 85 and 86 are under consideration.

Rejection under 35 U.S.C. §112, first paragraph

In the Office Action, claims 17, 18, 20, 67, 68, 70-73, 76-79, 85 and 86 were rejected under 35 U.S.C. §112, first paragraph allegedly for lack of enablement for several reasons which are discussed below.

First, the examiner contends the specification is not enabled for a polypeptide comprising a "heavy chain variable part" and a "light chain variable part." However, the examiner acknowledges that the specification is enabled "for a polypeptide capable of specific binding to factor VIII and interference with the activity of factor VIII inhibitors, wherein the polypeptide comprises a heavy chain variable **region** of a human antibody with factor VIII specificity and a light chain variable **region** of a human antibody and a composition thereof."

Merely in order to expedite prosecution, applicants have amended claims 17, 18, and 85 to reflect the polypeptide which the examiner has deemed to be enabled. Accordingly, applicants have replaced the word "part" with the word "region." In applicant's opinion, there is little difference between the meaning of the terms "variable part" and "variable region." Therefore, the amendments are not narrowing amendments.

Further, despite the arguments presented in the Amendment dated July 13, 2004, the examiner continues to question whether the composition of claims 20 and 81 would function as pharmaceutical compositions. In that Amendment, applicants pointed out to the examiner that the specification provides *in vitro* data demonstrating efficacy of the claimed invention in

neutralizing the activity of factor VIII inhibitors present in plasma of patients with haemophilia. Thus, a person skilled in the art would also expect efficacy *in vivo*.

In response, the examiner states that it has been established that in the absence of a correlation between the *in vitro* and *in vivo* efficacy the person having ordinary skill in the art has no basis for perceiving this efficacy.

For the reasons given below, applicants believe that an *in vivo* correlation has indeed been established between the presence of neutralizing antibodies directed against factor VIII (or factor VIII inhibitors) and reduced activity (or inactivity) of factor VIII.

As discussed in the background section of the instant application, a well-known problem associated with factor VIII replacement therapy of haemophilia A patients is the development of neutralizing antibodies directed against factor VIII. Several approaches have been tried to overcome this problem.

For example, it has been demonstrated *in vivo* that increasing the dosage of factor VIII or administering porcine factor VIII to haemophilia A patients can retain/restore factor VIII activity. See the background section of the application. However, the increasing dosage of factor VIII can cause the patient to develop factor VIII inhibitors. As a result, the patients requires increasingly higher dosages of factor VIII. Eventually, increasing the dosage is no longer effective.

Similarly, when porcine factor VIII is administered, the patient may develop porcine factor VIII inhibitors. Thus, the inhibitors may render the administration of porcine factor VIII ineffective.

The *in vitro* experiments in the application demonstrate that the claimed polypeptides are able to neutralize factor VIII inhibitors (from patients) and retain/restore factor VIII activity.

Thus, applicants believe that the above establishes a correlation between *in vitro* and *in vivo* efficacy.

Accordingly, applicants request that the rejection of the claims under 35 U.S.C. §112, be reconsidered and withdrawn.

Rejection under 35 U.S.C. §102 (b) over Davies et al.

Claims 17, 18, 70-73, 76-79 and 85-86 were rejected under 35 U.S.C. §102 (b) for allegedly being anticipated by Davies et al. The examiner states that Davies et al. teach eight human FVIII specific scFvs selected by panning on immobilized rFVIII. According to the examiner, Davies et al. further teach the method of producing recombinant scFv's specific for Factor VIII by obtaining the primary structure of the variable domains of factor VIII antibodies obtained from inhibitor patient B cells RNA by V gene phage display technology. Thus, the examiner contends that the polypeptides of Davies et al. are the same as the claimed polypeptides capable of specifically binding to FVIII and interference with FVIII inhibitors.

Applicants respectfully disagree. As mentioned in the previous response, Davies et al. discloses factor VIII specific scFv's. The scFv's of the present invention interfere with the activity of factor VIII inhibitors. However, Davies et al. is completely silent about whether the disclosed scFv's are capable of interfering with the activity of factor VIII inhibitors.

The examiner states that interference with the activity of factor VIII inhibitors is considered to be an inherent property of the scFv polypeptides disclosed in Davies et al. Applicants respectfully disagree.

In fact, not all scFv's to factor VIII have the claimed property (i.e., interference with the activity of factor VIII inhibitors). There is no recognition in Davies et al. to select scFv polypeptides that have this claimed property.

Further, the publication of Davies et al. is only an abstract, which did not lead to a publication. The abstract of Davies et al. does not provide an enabling disclosure for scFv's that are capable of interference with the activity of factor VIII inhibitors. Accordingly, the claimed invention can not be said to be anticipated by Davies et al.

For the above reasons, applicants respectfully request that the rejection of the claims under 35 U.S.C. §102(b) be reconsidered and withdrawn.

Rejection under 35 U.S.C. §103(a) over Davies et al. in view of U.S. Patent No. 4,731,245

Claim 20 was rejected under 35 U.S.C. §103(a) for allegedly being obvious over Davies et al. in view of U.S. Patent 4,731,245. Claim 20 is directed to a pharmaceutical composition comprising a polypeptides according to claims 17 or 18.

Accordingly to the examiner, the secondary reference (i.e., the '245 patent) discloses an antibody against a Streptococcus organism in a pharmaceutical carrier. Therefore, the examiner concludes that it would have been prima facie obvious to one of ordinary skill in the art to formulate the antibody fragments taught in Davies et al. in a composition with a pharmaceutically acceptable carrier as taught by the '245 patent.

Applicants respectfully disagree. Applicants have provided arguments to address the rejection of claims 17 and 18 over Davies et al. (see above). Therefore, claim 20 is patentable over Davies et al. at least for the same reasons that claims 17 and 18 are patentable. Specifically, there is no recognition in Davies et al. to select for polypeptides that have the activity of the claimed polypeptides (i.e., interference with activity of factor VIII inhibitors). Thus, the combination of Davies et al. and the '245 patent does not result in the claimed invention.

Accordingly, applicants respectfully request that the rejection of claim 20 under 35 U.S.C. §103(a) over Davies et al. in view of the '245 patent be reconsidered and withdrawn.

For the reasons given above, allowance of the pending claims is earnestly requested. If the examiner has any questions regarding this amendment, the examiner is invited to contact the undersigned at the telephone number listed below.

Respectfully submitted,

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